Test Definition: NSRGP

Noonan Syndrome and Related Panel,B

Overview

Useful For

Providing a comprehensive genetic evaluation for patients with a personal or family history suggestive of Noonan syndrome (NS) or related disorders

Establishing a diagnosis of a NS or related disorders, in some cases, allowing for appropriate management and surveillance for disease features based on the gene involved

Identifying variants within genes known to be associated with increased risk for disease features allowing for predictive testing of at-risk family members

Genetics Test Information

This test includes next-generation sequencing and supplemental Sanger sequencing to evaluate the genes tested on this panel.

Prior Authorization is available for this assay; see Special Instructions.

Highlights

This test uses next-generation sequencing to test for variants in the *BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, SHOC2,* and *SOS1* genes.

This test may aid in the diagnosis of Noonan syndrome, LEOPARD syndrome, cardiofaciocutaneous (CFC) syndrome, Costello syndrome, or a related disorder. This test cannot distinguish between germline variants associated with Noonan syndrome and related disorders versus somatic (oncogenic, nongermline) variants, which may be associated with hematologic neoplasms. Therefore, this test does not provide diagnostic, prognostic, or therapeutic information for somatic variants. Variants detected by this test are interpreted as germline unless otherwise noted in the interpretation.

Identification of a pathogenic variant may assist with prognosis, clinical management, familial screening, and genetic counseling.

Special Instructions

- Informed Consent for Genetic Testing
- Noonan Spectrum Gene Testing Patient Information Sheet
- Noonan Syndrome and Related Disorders Multi-Gene Panel Prior Authorization Ordering Instructions
- Informed Consent for Genetic Testing (Spanish)

Method Name

Custom Sequence Capture and Targeted Next-Generation Sequencing Followed by Polymerase Chain Reaction (PCR) and Supplemental Sanger Sequencing

NY State Available

Yes

Specimen

Specimen Type

Whole Blood EDTA

Ordering Guidance

Alternative testing designed to detect somatic variants associated with hematologic neoplasms is available; see NGSHM / OncoHeme Next-Generation Sequencing for Myeloid Neoplasms, Varies.

Targeted testing for familial variants (also called site-specific or known mutation testing) is available for the genes on this panel. See FMTT / Familial Mutation, Targeted Testing, Varies.

Necessary Information

1. Noonan Spectrum Gene Testing Patient Information Sheet **(T689) is required,** see Special Instructions. Testing may proceed without the patient information however it aids in providing a more thorough interpretation. Ordering providers are strongly encouraged to complete the form and send it with the specimen.

2. Include physician name and phone number with specimen.

Specimen Required

Container/Tube: Lavender top (EDTA)

Specimen Volume: 3 mL

Collection Instructions: Send specimen in original tube.

Additional Information: Prior Authorization is available for this assay; see Special Instructions. **Submit the required form with the specimen.**

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:

-Informed Consent for Genetic Testing (T576)

-Informed Consent for Genetic Testing-Spanish (T826)

2. Noonan Syndrome and Related Disorders Multi-Gene Panel Prior Authorization Ordering Instructions in Special Instructions

3. If not ordering electronically, complete, print, and send a Cardiovascular Test Request (T724) with the specimen.

Specimen Minimum Volume

1 mL

Reject Due To

No specimen should be rejected.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Whole Blood EDTA	Ambient (preferred)		
	Refrigerated		

Clinical and Interpretive

Clinical Information

Noonan syndrome (NS) is an autosomal dominant disorder of variable expressivity characterized by short stature, congenital heart defects, characteristic facial dysmorphology, unusual chest shape, developmental delay of varying degree, cryptorchidism, and coagulation defects, among other features.

Heart defects include pulmonary valve stenosis (20%-50%), hypertrophic cardiomyopathy (20%-30%), atrial septal defects (6%-10%), ventricular septal defects (approximately 5%), and patent ductus arteriosus (approximately 3%). Facial features, which tend to change with age, may include hypertelorism, downward-slanting eyes, epicanthal folds, and low-set and posteriorly rotated ears. Mild mental retardation is seen in up to one-third of adults.

The incidence of NS is estimated to be between 1 in 1,000 and 1 in 2,500, although subtle expression in adulthood may cause this number to be an underestimate. NS is genetically heterogeneous, with 4 genes currently associated with the majority of cases: *PTPN11, RAF1, SOS1,* and *KRAS.* Heterozygous variants in *NRAS*, *HRAS*, *BRAF*, *SHOC2*, *MAP2K1*, *MAP2K2*, and *CBL* have also been associated with a smaller percentage of NS and related phenotypes. All of these genes are involved in a common signal transduction pathway known as the Ras-mitogen-activated protein kinase (MAPK) pathway. The MAPK pathway is important for cell growth, differentiation, senescence, and death. Molecular genetic testing of all of the known genes identifies a variant in approximately 75% of affected individuals. NS can be sporadic and due to new variants; however, an affected parent can be recognized in 30% to 75% of families.

Some studies have shown that there is a genotype-phenotype correlation associated with NS. An analysis of a large cohort of individuals with NS has suggested that *PTPN11* variants are more likely to be found when pulmonary stenosis is present, while hypertrophic cardiomyopathy is commonly associated with *RAF1* variants, but rarely associated with *PTPN11.*

A number of related disorders exist that have phenotypic overlap with NS and are caused by variants in the same group of genes. *PTPN11* and *RAF1* variants have been associated with LEOPARD (lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and deafness) syndrome, an autosomal dominant disorder sharing several clinical features with NS. Variants in *BRAF, MAP2K1, MAP2K2,* and *KRAS* have been identified in individuals with cardiofaciocutaneous (CFC) syndrome, a condition involving congenital heart defects, cutaneous abnormalities, Noonan-like facial features, and severe psychomotor developmental delay. Costello syndrome, which is characterized by coarse facies, short stature, distinctive hand posture and appearance, severe feeding difficulty, failure to thrive, cardiac anomalies, and developmental disability has been primarily associated with variants in *HRAS*. Variation in *SHOC2* has been associated with a distinctive phenotype involving features of NS and loose anagen hair.

Genes included in the Noonan Syndrome and Related Disorders Multi-Gene Panel

Gene	Protein	Inheritance	Disease Association
BRAF	V-RAF murine sarcoma viral oncogene homolog b1	AD	Noonan/CFC/Costello syndrome
CBL	CAS-BR-M murine ecotropic retroviral transforming sequence homolog	AD	Noonan syndrome-like disorder

HRAS	V-HA-RAS Harvey rat sarcoma viral oncogene homolog	AD	Costello syndrome
KRAS	V-KI-RAS Kirsten rat sarcoma viral oncogene homolog	AD	Noonan/CFC/Costello syndrome
MAP2K1	Mitogen-activated protein kinase kinase 1	AD	Noonan/CFC
MAP2K2	Mitogen-activated protein kinase kinase 2	AD	Noonan/CFC
NRAS	Neuroblastoma ras viral oncogene homolog	AD	Noonan syndrome
PTPN11	Protein-tyrosine phosphatase, nonreceptor-type, 11	AD	Noonan/CFC/LEOPARD syndrome
RAF1	V-raf-1 murine leukemia viral oncogene homolog 1	AD	Noonan/LEOPARD syndrome
SHOC2	Suppressor of clear, c. Elegans, homolog of	AD	Noonan-syndrome like with loose anagen hair
SOS1	Son of sevenless, drosophila, homolog 1	AD	Noonan-syndrome like with loose anagen hair

Abbreviations: Autosomal dominant (AD)

Reference Values

An interpretive report will be provided.

Interpretation

Evaluation and categorization of variants is performed using the most recent published American College of Medical Genetics and Genomics (ACMG) recommendations as a guideline. Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Multiple in silico evaluation tools may be used to assist in the interpretation of these results. The accuracy of predictions made by in silico evaluation tools is highly dependent upon the data available for a given gene, and predictions made by these tools may change over time. Results from in silico evaluation tools should be interpreted with caution and professional clinical judgment.

Cautions

Clinical Correlations:

Some individuals who have involvement of 1 or more of the genes on the panel may have a variant that is not identified by the methods performed (eg, promoter variants, deep intronic variants). The absence of a variant, therefore, does not eliminate the possibility of Noonan syndrome (NS) or a related disorder.

Test results should be interpreted in context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

If testing was performed because of a family history of NS or a related disorder, it is often useful to first test an affected family member. Identification of a pathogenic variant in an affected individual would allow for more informative testing of at risk individuals.

If clinical or family history suggests that a detected variant may be somatic and not germline, additional genetic testing of alternate tissue types or appropriate counseling and medical management may be indicated. In addition, a negative result does not preclude the presence of a somatic variant at low (<10%) variant allele frequency.

Technical Limitations:

Next-generation sequencing may not detect all types of genetic variants. Additionally, rare polymorphisms may be present that could lead to false-negative or false-positive results. If results do not match clinical findings, consider alternative methods for analyzing these genes, such as Sanger sequencing or large deletion/duplication analysis. If the patient has had an allogeneic blood or marrow transplant or a recent (ie, less than 6 weeks from time of sample collection) heterologous blood transfusion these results may be inaccurate due to the presence of donor DNA.

Reclassification of Variants Policy:

At this time, it is not standard practice for the laboratory to systematically review likely pathogenic variants or variants of uncertain significance that are detected and reported. The laboratory encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time.

Contact the laboratory if additional information is required regarding the transcript or human genome assembly used for the analysis of this patient's results.

Clinical Reference

1. Tartaglia M, Gelb BD, Zenker M: Noonan syndrome and clinically related disorders. Best Pract Res Clin Endocrinol Metab. 2011;25(1):161-179

2. Rauen KA: Cardiofaciocutaneous Syndrome. In: Pagon RA, Adam MP, Ardinger HH, et al, eds. GeneReviews. University of Washington, Seattle. 1993-2018. 2007 Jan 18 (Updated 2016 Mar 3). Accessed February 2018. Available at www.ncbi.nlm.nih.gov/books/NBK1186/

3. Allanson JE, Roberts AE: Noonan Syndrome. In: Pagon RA, Adam MP, Ardinger HH, et al, eds. GeneReviews. University of Washington. Seattle. 1993-2018. 2001 Nov 15 (Updated 2016 Feb 25). Accessed February 2018. Available at www.ncbi.nlm.nih.gov/books/NBK1124/

4. Gripp KW, Lin AE: Costello Syndrome. In: Pagon RA, Adam MP, Ardinger HH, et al, eds. GeneReviews. University of Washington, Seattle. 1993-2018. 2006 Aug 29 (Updated 2012 Jan 12). Accessed February 2018. Available at www.ncbi.nlm.nih.gov/books/NBK1507/

5. Gelb BD, Tartaglia M: Noonan Syndrome with Multiple Lentigines. In: Pagon RA, Adam MP, Ardinger HH, et al, eds. GeneReviews. University of Washington, Seattle. 1993-2018. 2007 Nov 30 (Updated 2015 May 14) Accessed February 2018. Available at www.ncbi.nlm.nih.gov/books/NBK1383/

Performance

Method Description

Next-generation sequencing (NGS) is performed using an Illumina instrument with paired-end reads. The DNA is prepared for NGS using a custom Agilent SureSelect Target Enrichment System. Data is analyzed with a bioinformatics software pipeline. Supplemental and/or confirmatory Sanger sequencing is performed when

necessary.(Unpublished Mayo method)

The following genes are evaluated in this multigene panel: *BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, SHOC2,* and *SOS1.*

PDF Report

No

Day(s) Performed

Monday

Report Available

2 to 4 weeks after prior authorization approved

Specimen Retention Time

Extracted DNA: 2 months

Performing Laboratory Location

Rochester

Fees and Codes

Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information

81479-CBL

81404-HRAS

81311-NRAS

81405 x 2-KRAS, SHOC2

81406 x 6-BRAF, MAP2K1, MAP2K2, PTPN11, RAF1, SOS1

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
NSRGP	Noonan Syndrome and Related Panel,B	In Process

Result ID	Test Result Name	Result LOINC Value
36821	Gene(s) Evaluated	48018-6
36822	Result Summary	50397-9
36823	Result Details	82939-0
36824	Interpretation	59462-2
36953	Additional Information	48767-8
36954	Method	85069-3
36955	Disclaimer	62364-5
36825	Reviewed by	18771-6

Prior Authorization

Insurance preauthorization is available for this testing; forms are available in Special Instructions.

Patient financial assistance may be available to those who qualify.Patients who receive a bill from Mayo Clinic Laboratories will receive information on eligibility and how to apply.